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A systematic review and meta-analysis of 18F-labeled amyloid imaging in Alzheimer's disease

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Neuroimaging

A systematic review and meta-analysis of ^{18}F -labeled amyloid imaging in Alzheimer's diseaseJing Ming Yeo^a, Briony Waddell^{b,c}, Zubair Khan^d, Suvankar Pal^{b,c,e,*}^aCollege of Medicine and Veterinary Medicine, University of Edinburgh, Edinburgh, UK^bAnne Rowling Regenerative Neurology Clinic, University of Edinburgh, Edinburgh, UK^cDivision of Clinical Neurosciences, Western General Hospital, Edinburgh, UK^dDepartment of Nuclear Medicine, NHS Lothian, Edinburgh, UK^eDepartment of Neurology, Forth Valley Royal Hospital, NHS Forth Valley, Larbert, UK**Abstract****Background:** Amyloid imaging using fluorine 18-labeled tracers florbetapir, florbetaben, and flutemetamol has recently been reported in Alzheimer's disease (AD).**Methods:** We systematically searched MEDLINE and EMBASE for relevant studies published from January 1980 to March 2014. Studies comparing imaging findings in AD and normal controls (NCs) were pooled in a meta-analysis, calculating pooled weighted sensitivity, specificity, and diagnostic odds ratio (OR) using the DerSimonian-Laird random-effects model.**Results:** Nineteen studies, investigating 682 patients with AD, met inclusion criteria. Meta-analysis demonstrated a sensitivity of 89.6%, a specificity of 87.2%, and an OR of 91.7 for florbetapir in differentiating AD patients from NCs, and a sensitivity of 89.3%, a specificity of 87.6%, and a diagnostic OR of 69.9 for florbetaben. There were insufficient data to complete analyses for flutemetamol.**Conclusions:** Results suggest favorable sensitivity and specificity of amyloid imaging with fluorine 18-labeled tracers in AD. Prospective studies are required to determine optimal imaging analysis methods and resolve outstanding clinical uncertainties.© 2015 Published by Elsevier Inc. on behalf of the Alzheimer's Association. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).**Keywords:**

Alzheimer's; Dementia; Amyloid; Positron emission tomography; Florbetapir; Florbetaben; Flutemetamol; Sensitivity; Specificity

1. Introduction

Timely diagnosis of dementia obviates prolonged uncertainty, unnecessary investigations, delays in initiation of symptomatic treatments, and recruitment of poorly characterized patients into research trials. Definitive diagnosis may only be achieved by histopathological examination of invasive brain biopsy or postmortem tissue, or molecular genetic testing in a minority with inherited dementia. Clinical diagnostic criteria in recent use for Alzheimer's disease (AD) often fail to robustly differentiate accurately between

AD and non-AD pathology with up to 40% of patients diagnosed with non-AD dementias identified as having pathology consistent with AD at postmortem in some series [1]. Clinical diagnosis either provides good diagnostic sensitivity at the expense of specificity or vice versa (pooled averages 81% sensitive and 70% specific) [2].

When considering the pathophysiology of AD, it has been proposed that the presymptomatic phase is characterized by an early rise in amyloid accumulation, followed later by synaptic dysfunction, tau-mediated neuronal injury, reduction in brain volume, and finally emergence of cognitive symptoms, followed by a clinical syndrome of frank dementia [3]. This suggests a sensitive and specific biomarker of brain amyloid deposition, such as amyloid imaging, would be a useful diagnostic tool, perhaps as an adjunct to investigation of

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cerebrospinal fluid (CSF) biomarkers (including amyloid and tau), cerebral hypometabolism ascertained by ^{18}F -fluorodeoxyglucose positron emission tomography, hippocampal volume, tractography, and clinical cognitive assessments.

The most widely studied radiolabeled amyloid ligand, ^{11}C -labeled Pittsburgh compound B (^{11}C -PiB), demonstrates high affinity and selective amyloid binding. Imaging using ^{11}C -PiB has been reported to successfully differentiate between patients with AD and healthy controls [4], predict the progression of mild cognitive impairment (MCI) to symptomatic AD [5], and correlate with underlying amyloid neuropathology [6]. Disadvantages include a radioactive decay half-life of only 20 minutes and a scanning time of 30 minutes, rendering it limited to use in centers with cyclotrons, which are expensive and impractical, thereby limiting its utility in clinical settings.

The proven efficacy of amyloid imaging and impracticalities of ^{11}C -PiB triggered a search to identify compounds with desirable qualities of high affinity for amyloid, rapid brain uptake and washout from non-amyloid-containing tissues, short imaging time, and long stable pseudoequilibrium allowing flexibility in imaging acquisition time. Amyloid imaging using three novel fluorine 18-labeled (^{18}F) tracers, ^{18}F -florbetapir, ^{18}F -florbetaben, and ^{18}F -flutemetamol, with a longer half-life than ^{11}C -PiB of 110 minutes has recently been investigated in a number of studies, including phase 2 clinical trials. These agents have recently gained US Food and Drug Administration approval for use in clinical practice. The benefits of identifying amyloid in vivo extend to monitoring disease progression, and, with the advent of treatments targeting amyloid deposition, potentially also as a surrogate biomarker of treatment efficacy.

In this systematic review and meta-analysis, we (1) assess the quality of recent studies investigating amyloid imaging using novel fluorine-labeled tracers, (2) investigate their pooled reported sensitivity and specificity for diagnosis of AD, and (3) consider the utility of amyloid imaging using these agents in the differential diagnosis of dementia syndromes.

2. Methods

2.1. Search strategy and study selection

We searched the Medical Literature Analysis and Retrieval System Online (MEDLINE) and the Excerpta Medica Database (EMBASE) via OVID for human studies published from January 1980 to March 2014, inclusive of all languages. The search terms used were (1) “dementia,” (2) “amyloid” or “positron emission tomography,” (3) “florbetapir” or “florbetaben” or “flutemetamol,” and (3) “sensitivity” and “specificity” or “diagnosis.” The inclusion criteria were as follows: (1) original study; (2) study of diagnostic accuracy of florbetapir/florbetaben/flutemetamol amyloid imaging; (3) the study compares clinically or

pathologically diagnosed dementia (AD, frontotemporal dementia [FTD], vascular dementia [VD], dementia with Lewy bodies [DLB] with each other or with normal controls; (4) amyloid imaging was not interpreted with other imaging modality; (5) total subjects in the study of at least 10; and (6) sufficient data were reported to enable a 2×2 contingency table to be formulated for the calculation of sensitivity and specificity. Two authors applied these inclusion criteria independently in identifying the studies.

2.2. Data extraction

We extracted data on the author's name, year of publication, amount of ligand injected per scan, method of image analysis, criteria used for defining a positive amyloid scan, criteria used for clinical or pathological diagnosis, study population characteristics (mean age, mean Mini-Mental State Examination [MMSE] score), internal and external validity score, and constructed a 2×2 contingency table for each study. (1) True positive was defined as patients with AD who had positive amyloid imaging, (2) false negative: patients with AD who had negative amyloid imaging, (3) true negative: diagnostic comparison group patients with negative amyloid imaging, and (4) false positive: diagnostic comparison group patients with positive amyloid imaging. In studies where there were more than one relevant data set, we chose the data set with (1) the most relevant clinical diagnosis (probable and definite AD, as opposed to possible AD), (2) quantitative analysis, rather than visual analysis, (3) age-matched normal controls (NCs) (when there were both young and older normal controls), and (4) data set in which intermediate result was reported.

2.3. Quality assessment

Our study is reported in accordance with the PRISMA guidelines; a completed PRISMA checklist is available as [Appendix 1](#) [7]. Our assessment of the internal and external validity of individual studies is detailed in [Appendix 2](#); assessment was based on the STARD checklist, and in particular items 3 to 5, 7, 11 to 13, 15, 16, 18, 21, 22, and 25 [8].

2.4. Data synthesis and statistical analysis

We calculated the sensitivity and specificity of the relevant diagnostic comparison groups for each included study. We also pooled the studies comparing amyloid imaging in AD patients and NCs for florbetapir and florbetaben in a meta-analysis using Meta-DiSc (Javier Zamora, Boston, MA, USA) software for statistical analysis [9]. For this, we calculated the pooled weighted sensitivity, specificity, positive and negative likelihood ratios (LRs), and diagnostic odds ratio (OR) for AD patients versus NC using DerSimonian-Laird random-effects model. This model recognizes both between- and within-study heterogeneity and considers the different effect sizes of the studies, thus

allowing the results to be applied to a wider range of studies [10]. For the log OR of any 2×2 table with zero, the software would add 0.5 to each cell. We assessed for between-study heterogeneity using I^2 and χ^2 test, where an $I^2 > 50\%$ and a P value $< .05$ indicate a significant amount of heterogeneity unlikely to be explained by random variation alone [11]. We further investigated the heterogeneity using a summary receiver operating characteristic curve to describe a set of operating characteristics across the studies and used Spearman correlation coefficient to look for a threshold effect. A positive Spearman correlation coefficient between logit of sensitivity and logit of $1 - \text{specificity}$ would suggest the possibility of a threshold effect, caused by the different studies using different diagnostic thresholds to determine a positive or negative result. We also used single-factor meta-regression analysis to look for possible sources of heterogeneity using the following variates as predictor variables: (1) mean age; (2) mean MMSE score; (3) male-female distribution; and (4) method of image analysis (visual vs. quantitative). A variate is considered to be explanatory if the regression coefficient was statistically significant ($P < .05$).

3. Results

Our literature search produced a total of 86 articles (Fig. 1). We excluded 66 articles after reading the abstracts and reviewed the remaining 23 full-text articles, after which a further six articles were excluded. We identified two additional articles from reviews and references, bringing the review to a total of 19 articles. Table 1 summarizes the number and mean age of subjects in the included studies. Table 2 specifies the data collected from each study. The review revealed that most of the available studies' diagnostic comparison groups were AD patients versus NCs; therefore, we performed a meta-analysis investigating these groups. Relevant data pertaining to other dementias were also included for the consideration of diagnostic utility (Table 2). Table 3 summarizes the pooled weighted sensitivity, specificity, LR, and diagnostic ORs for AD patients versus NCs for florbetapir and florbetaben. The pooled diagnostic ORs and positive LR and their confidence intervals (CIs) were all above 1, suggesting that florbetapir and florbetaben amyloid imaging have diagnostic utility in this group.

3.1. Florbetapir

There were 10 studies identified in this group, with nine studies comparing the diagnostic utility of AD versus NC and one study comparing AD versus non-AD (which included FTD, VD, alcohol-related dementia, corticobasal degeneration, depression, structural causes, and dementia of uncertain etiology). Two studies, Clark et al. [13] and Doraiswamy et al. [15], were prospective cohort studies, whereas the rest were case-control studies. The study by Clark et al. was the only one with a neuropathological diag-

nosis, demonstrating a very favorable sensitivity of 97.5% and specificity of 100% in differentiating AD patients from NCs. Fleisher et al. [16], Fleisher et al. [17], Doraiswamy et al. [15], and Grundman et al. [18] recruited patients from the same multicenter nonrandomized phase I and II trials of florbetapir PET imaging; therefore, only the study by Fleisher et al. [16] with the most complete number of patients was included in the meta-analysis for AD patients versus NCs.

For the meta-analysis, seven studies were included, with a total number of 181 patients with AD (combined mean age, 71.8 years [95% CI: 67.4–76.2], combined mean MMSE score, 21.0 [95% CI: 18.7–23.1]) and 197 NCs (combined mean age, 68.3 years [95% CI: 64.5–72.2], combined mean MMSE score, 29.2 [95% CI: 28.8–29.6]). The meta-analysis revealed a pooled weighted sensitivity of 89.6%, a pooled weighted specificity of 87.2%, and a pooled diagnostic OR of 91.7 for differentiating AD patients from NCs. For the pooled diagnostic OR, heterogeneity was present between the studies, and although the CI did not contain the value of 1, it was wide, suggesting that more studies with larger sample sizes are required for a more definite conclusion on the strength of this diagnostic utility. Spearman correlation coefficient was -0.927 ($P = .003$) suggesting the absence of a threshold effect. Single-factor meta-regression analysis for other possible sources of heterogeneity did not show any significant association between the variates described previously and log OR. This heterogeneity may contribute to an underestimation of the discriminatory ability of florbetapir.

3.2. Florbetaben

Six case-control studies were identified in this group. Barthel et al. [24] reported on the use of florbetaben PET imaging in a multicenter phase II trial in patients with AD and NCs, finding a sensitivity of 85% and a specificity of 91%. It found that regional standard uptake value ratios (SUVRs) were significantly higher in the frontal, temporal, parietal, occipital, and anterior and posterior cingulate cortices in patients with AD compared with NCs. An ongoing phase III trial on florbetaben PET imaging for detecting in vivo β -amyloid using histopathology as the gold standard is estimated to be completed later this year [33]. Schipke et al. [25] and Tiepolt et al. [26] recruited patients from the phase II trial and were therefore excluded from the meta-analysis.

For the meta-analysis, four studies were included, with a total number of 131 patients with AD (combined mean age, 70.6 years [95% CI: 67.9–73.3], combined mean MMSE score, 21.8 [95% CI: 19.2–24.3]) and 121 NCs (combined mean age, 69.1 years [95% CI: 66.3–71.9], combined mean MMSE score, 29.4 [95% CI: 29.0–29.8]). The meta-analysis resulted in a pooled weighted sensitivity of 89.3%, a pooled weighted specificity of 87.6%, and a pooled diagnostic OR of 69.9, with no significant heterogeneity (all

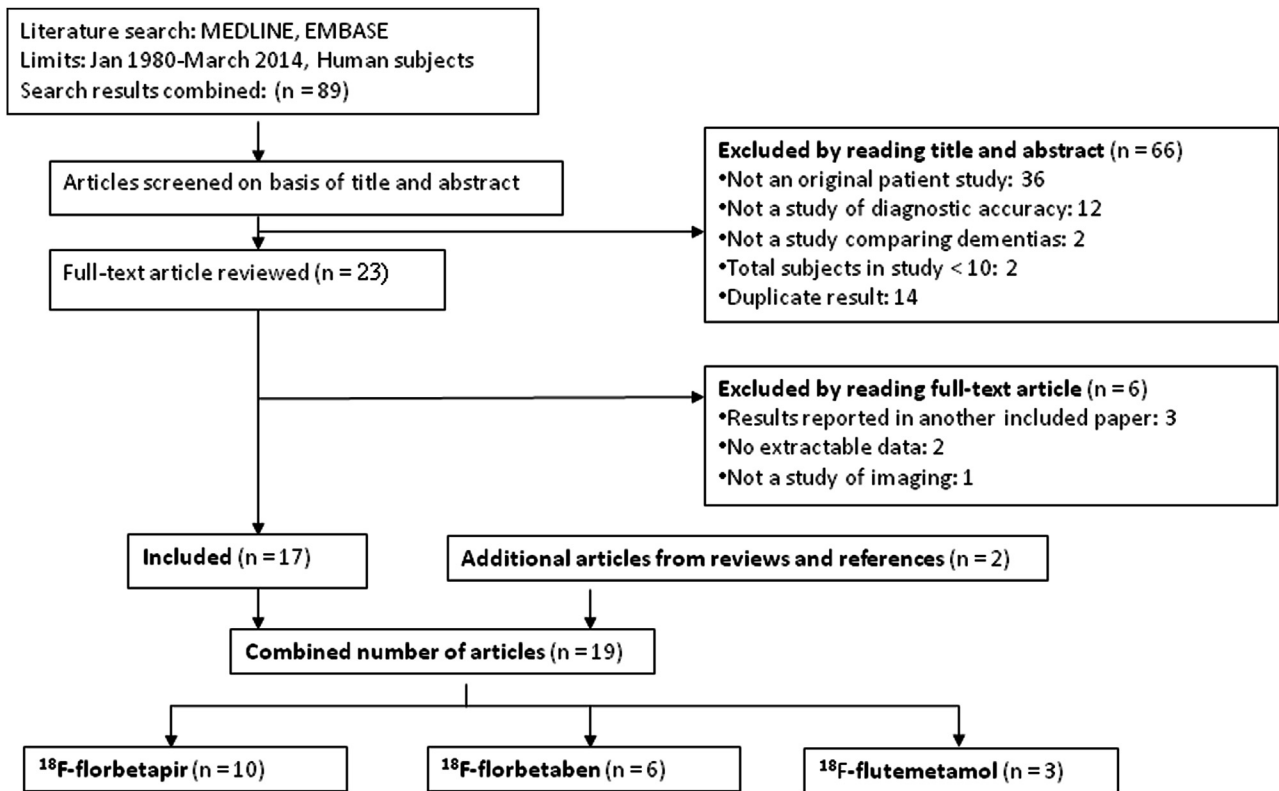


Fig. 1. Flow chart of study selection.

$I^2 < 50\%$ and P values $< .05$). However, the wide CI for the diagnostic OR again suggests the need for further and larger studies to be conducted.

3.3. Flutemetamol

There were three studies in this group, with the study by Nellissen et al. [32] being a phase I trial and the study by Vandenberghe et al. [31] being a phase II trial for flutemetamol PET imaging in AD. Results were encouraging, with the phase II trial demonstrating a sensitivity of 92.6% and specificity of 96.0% in differentiating AD patients from NCs. The study by Duara et al. [30] was an extension of the phase II trial, which demonstrated the additive value of structural magnetic resonance imaging to the diagnostic classification of prodromal and probable AD. Flutemetamol is structurally identical to ^{11}C -PiB except for the presence of $3'$ ^{18}F -fluorine, making it unique compared to the other fluorine tracers. A trial is ongoing on the distribution

of ^{11}C -PiB and flutemetamol in regions of cerebral amyloid deposition in AD, with the hypothesis that there will be no significant difference between the two [34].

4. Discussion

Clinical diagnostic criteria in recent use for AD (including iterations of the Diagnostic and Statistical Manual of Mental Disorders and International Classification of Diseases) have variable specificity and sensitivity with pooled averages of 70% and 81%, respectively, when compared with postmortem data [2]. The National Institute on Aging and the Alzheimer's Association work groups have recently revised the NINCDS-ADRDA criteria for AD to incorporate biomarkers in an attempt to improve diagnostic accuracy [35]. A dynamic change in biomarker profiles during the evolution of AD progression has been postulated with early deposition of β -amyloid followed by

Table 1
Summary of all studies

Amyloid imaging	Number of studies	Alzheimer's disease		Non-Alzheimer's disease	
		Number	Combined mean age, y (95% CI)	Number	Combined mean age, y (95% CI)
Florbetapir	10	343	72.5 (68.2–76.8)	348	68.2 (64.5–71.9)
Florbetaben	6	277	70.7 (68.2–73.2)	253	68.5 (66.0–71.1)
Flutemetamol	3	62	69.3 (67.1–71.4)	38	66.6 (62.3–71.0)

Abbreviation: CI, confidence interval.

Table 2
Characteristics of individual studies

		Quality*		Imaging method			Diagnosis	Study population				Outcome measure	
Study	Year	Internal	External	Amount MBq	Image analysis	Definition positive amyloid scan SUVR threshold	Diagnostic criteria	Number	Mean age (SD)	Mean MMSE (SD)	Male/female	Sensitivity (%)	Specificity (%)
Florbetapir													
Camus et al. [12]	2012	9	4	259 ± 57	Quantitative	>1.122	NINCDS, DSM-IV	13 AD 21 NC	67.8 (6.5) 66.2 (4.3)	23.0 (3.6) 29.0 (1.3)	4/9 9/12	92.3	90.5
Clark et al. [13,14]	2012	9	3	370	Quantitative	>1.10	Pathological	39 AD 10 NC	All 79.4 (12.6)	NR	NR	97.4	100
Doraiswamy et al. [15]	2012	9	4	370	Visual	Cortical uptake	NINCDS, MMSE≤24	31 AD 69 NC	76.7 69.8	21.4 29.6	28/41 18/13	67.7	85.5
Fleisher [16]	2011	9	4	370	Quantitative	≥1.17	NINCDS, M10-24	68 AD 82 NC	74.6 (9.5) 71.8 (10)	19.9 (4.4) 29.6 (0.5)	16/33 10/45	80.9	79.3
Fleisher et al. [17]	2013	9	4	370	Quantitative	>1.083	NINCDS, M10-24	45 AD 61 NC	74.7 (9.0) 67.9 (11.3)	20.6 (4.3) 29.6 (0.5)	22/23 27/34	84	75.4
Grundman et al. [18]	2013	9	2	370	Visual	NR	Clinical judgment	86 AD 21 non-AD	NR	NR	NR	61.6	57.1
Joshi et al. [19]	2012	9	4	370	Visual	Cortical uptake	NINCDS, M10-24	9 AD 11 NC	70.3 44.4	20.9 29.7	2/8 6/4	100	100
La Joie et al. [20]	2012	9	3	4 MBq/kg	Quantitative	>1.1	NINCDS	22 AD 37 NC	NR	NR	NR	90.9	91.9
Newberg et al. [21]	2012	9	3	370	Visual	Cortical uptake	NINCDS	19 AD 21 NC	73 (9) 67 (13)	20 (7) 29 (1)	8/11 13/8	94.7	95.2
Wong et al. [22]	2010	9	2	370	Visual	Cortical uptake	NINCDS, M10-24	11 AD 15 NC	NR	NR	NR	90.9	86.7
Florbetaben													
Barthel et al. [23]	2011	9	3	300	Visual	Cortical uptake	NINCDS, DSM-IV	10 AD 10 NC	69 (7) 67 (8)	19 (7) 29 (1)	8/2 8/2	90	90
Barthel et al. [24], phase II trial	2011	9	4	300	Quantitative	Linear discriminate function analysis of regional SUVRs	NINCDS, DSM-IV	81 AD 69 NC	70.7 (7.8) 68.2 (6.9)	22.6 (2.3) 29.3 (0.8)	47/34 30/39	85	91
Schipke et al. [25]	2012	9	3	NR	NR	NR	NINCDS, DSM-IV	121 AD, 80 NC	NR	NR	NR	81.8	82.5
Tiepol et al. [26]	2012	9	3	300 ± 60	Visual	Cortical uptake	NINCDS, DSM-IV	25 AD 25 NC	70.9 (8.0) 67.1 (7.7)	22.5 (2.2) 29.2 (0.8)	14/11 14/11	80	96
Villemagne et al. [27,28]	2011	9	4	300	Visual	Cortical uptake	NINCDS, Consensus criteria FTD	30 AD 32 NC 11 FTD 7 DLB 4 VD 5 PD	72.0 (9.2) 70.7 (6.3) 63.5 (7.0) 71.7 (5.7) 73.0 (11.0) 72.6 (6.5)	22.8 (3.7) 29.6 (0.7) 24.5 (2.9) 24.0 (6.6) 27.8 (2.1) 27.4 (2.7)	14/16 19/13 7/4 7/0 0/4 5/0	96.7 96.7 96.7 96.7 96.7	84.4 90.9 71.4 75.0 100
Villemagne et al. [29]	2012	9	4	300	Visual	Cortical uptake	NINCDS	10 AD 10 NC	70.8 (9.6) 70.4 (7.2)	22.7 (3.9) 29.6 (0.7)	8/2 6/4	100	70
Flutemetamol													
Duara et al. [30]	2013	9	4	185	Quantitative	>1.56 >1.40	NINCDS, DSM-IV	27 AD 15 NC	69.6 (7.0) 68.7 (7.6)	23.3 (2.2) 28.8 (1.0)	12/15 9/6	92.6 92.6	93.3 80
(Continued)													

(Continued)

Table 2
Characteristics of individual studies (Continued)

Study	Quality*			Imaging method		Diagnosis	Study population			Outcome measure				
	Year	Internal	External	Amount MBq	Image analysis		Definition positive amyloid scan SUVR threshold	Diagnostic criteria	Number	Mean age (SD)	Mean MMSE (SD)	Male/female	Sensitivity (%)	Specificity (%)
Vandenberghe et al. [31], phase II Nelissen et al. [32], phase I	2010	9	3	185	Visual	Cortical uptake	NINCDS, DSM-IV	27 AD	69.6 (7.0)	23.3 (2.2)	12/15	92.6	96	
								15 NC	68.7 (7.6)	29.4 (1.0)	9/6			
	2009	9	2	180	Visual, Quantitative	Cortical uptake	NINCDS, DSM-IV	8 AD	68.6 (6.9)	23.1 (1.9)	6/2	75.0	87.5	
								8 NC	62.5 (7.1)	28.9 (1.0)	5/3			
Abbreviations: SUVR, standard uptake value ratio; SD, standard deviation; MMSE, Mini-Mental State Examination; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders; AD, Alzheimer's disease; NC, normal control; NR, not reported; FTD, frontotemporal dementia; DLB, dementia with Lewy bodies; VD, vascular dementia; PD, Parkinson's disease.														

Abbreviations: SUVR, standard uptake value ratio; SD, standard deviation; MMSE, Mini-Mental State Examination; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders; AD, Alzheimer's disease; NC, normal control; NR, not reported; FTD, frontotemporal dementia; DLB, dementia with Lewy bodies; VD, vascular dementia; PD, Parkinson's disease.

NOTE: Studies in bold were included in the meta-analysis.

*Please see Appendix 2.

neuronal degeneration [3]. Cerebral PET amyloid imaging uses tracers that bind to fibrillar β -amyloid plaques and is able to estimate neuritic amyloid plaque burden [4]. This is the first systematic review and meta-analysis to investigate the diagnostic utility of florbetapir, florbetaben, and flutemetamol as biomarkers of amyloid deposition in AD.

Our results demonstrate a pooled weighted sensitivity of 89.6%, a pooled weighted specificity of 87.2%, and a pooled diagnostic OR of 91.7 for florbetapir in differentiating AD patients from NCs. Investigation of florbetaben demonstrated similar results with a pooled weighted sensitivity of 89.3%, a specificity of 87.6%, and a pooled diagnostic OR of 69.9. There were insufficient data to provide pooled statistical analysis of the diagnostic utility of flutemetamol. These results therefore suggest favorable sensitivity and specificity of fluorine-based tracers when compared to clinical diagnosis and other biomarkers commonly used in practice [21] and are comparable to ^{11}C -PiB imaging, with, in addition, good patient tolerability demonstrated [23]. When considering the pooled diagnostic OR, heterogeneity was present between studies, with wide CIs suggesting the need for more and better powered studies. All the studies assessed had good internal validity, reflecting that a causal relationship has been satisfactorily demonstrated and that confounding factors were controlled for as far as possible.

There are, however, a number of important limitations in studies evaluated in this systematic review which must be considered before it can be concluded that amyloid imaging with fluorine-based tracers should be introduced as a routine in the investigation of suspected AD. Although all studies scored highly on measures of internal validity, 10 studies did not score maximum points on external validity; most of these did not report on comorbidities and exclude patients accordingly. The number of subjects included in each study was low, and the number of studies per tracer was limited (Table 2), most notably in the flutemetamol group. Different diagnostic criteria were applied across the studies, adding to interstudy heterogeneity. Pharmaceutical funding of included studies may feasibly have introduced bias.

Characterization of cognitive impairment was variable and somewhat limited in most studies, with MMSE reported in the majority. MMSE is notably easy to administer with high test-retest reliability but lacks diagnostic specificity in AD [36], as demonstrated by the overlap of MMSE scores between those diagnosed with MCI and healthy controls [30] and those with AD and MCI [27]. Some of the studies did use more detailed cognitive batteries, but details of results are not reported in sufficient detail to allow evaluation in a meta-analysis [19,23,26,29].

Only one study correlated imaging findings with histopathological confirmation of AD at postmortem [13], demonstrating a high sensitivity and specificity of 92% and 100%, respectively, for florbetapir. Although these results are encouraging, study inclusion criteria required a predicted life expectancy of less than 6 months, limiting generalizability of these results.

Table 3

Summary of pooled weighted sensitivity, specificity, positive and negative likelihood ratios, and diagnostic odds ratio for Alzheimer's disease versus normal controls

	Sensitivity (%)	Specificity (%)	LR+	LR–	Diagnostic OR
Florbetapir (n = 7)					
Pooled estimates	89.6	87.2	7.90	0.108	91.7
95% CI	84.2–93.6	81.7–91.6	4.23–14.8	0.055–0.213	26.7–315
I ² value, %	46.2	50.3	38.9	35.7	53.5
Chi-squared (P value)	11.2 (P = .084)	12.1 (P = .060)	9.82 (P = .132)	9.34 (P = .155)	12.9 (P = .045)
Florbetaben					
Pooled estimates	89.3	87.6	6.06	0.141	69.9
95% CI	82.7–94.0	80.4–92.9	3.36–10.9	0.087–0.228	29.6–165
I ² value, %	48.6	13.4	34.8	0.0	0.0
Chi-squared (P value)	5.83 (P = .120)	3.46 (P = .326)	4.60 (P = .203)	2.61 (P = .456)	0.68 (P = .879)

Abbreviations: LR+, positive likelihood ratio, LR–, negative likelihood ratio; OR, odds ratio; CI, confidence interval.

APOE $\epsilon 4$ status is a known risk factor for cerebral amyloid deposition and for the development of AD. *APOE* $\epsilon 4$ status was demonstrated to significantly influence amyloid imaging results [12,17,24] (with Camus et al. [12] demonstrating this as the only significant variable). Reporting of *APOE* $\epsilon 4$ status was incomplete across studies, and no statistical adjustment was made for results. Furthermore, the significance of amyloid deposition in asymptomatic *APOE* $\epsilon 4$ –positive individuals remains extremely uncertain because of a lack of longitudinal data on natural history in such cases.

A fundamental limitation of amyloid imaging is the lack of specificity of amyloid burden in AD. Amyloid deposition has been implicated in a range of neurodegenerative disorders, including common differential diagnoses for AD, such as DLB and some pathological subtypes of primary progressive aphasia. Villemagne et al. [27] investigated the potential of amyloid imaging in differentiating between patients with FTDs, VD, DLB, Parkinson's disease, MCI, and healthy controls. Differences were only demonstrated between AD and healthy controls (and MCI and healthy controls). Because of small numbers in the subgroup analyses, robust conclusions cannot be drawn about the role of these tracers in the differential diagnosis of dementia without further clarification from larger and better powered studies.

Methods for scan interpretation differed between studies evaluated in this meta-analysis and included visual and quantitative analysis (Table 2). Although quantitative image analysis should feasibly provide a more objective outcome measure, SUVR cutoff varied, with only one study using a SUVR cutoff calculated from patients with postmortem-proven AD and healthy *APOE* $\epsilon 4$ negative as controls (Fletcher et al. [16]). Visual interpretation varied between studies, with Camus et al. [12] reporting 31% specificity for AD; however, Clark et al. [13] demonstrated a strong correlation between visual review of images and histopathological diagnosis.

Results from our meta-analysis do not enable recommendations to be made regarding transformation of MCI to AD in clinical practice. Doraiswamy et al. [15] provide limited longitudinal data to address this question with a suggestion

that positive amyloid imaging in patients with MCI confers a greater risk of progression in MMSE scores. Follow-up, however, was limited to a period of 18 months, and therefore, further prospective longitudinal studies are required to clarify this observation. It is also unknown whether the sensitivity of amyloid imaging varies according to disease stage. Duara et al. [30] found a lower rate of positive amyloid scans among patients with MCI compared with those with AD (50% vs. 93%). Without standardized SUVR reference ranges or further studies assessing prodementia phases of AD, it is currently not possible to conclude whether disease stage-specific SUVR thresholds are required to improve the detection of early-phase AD.

The mean age of subjects with AD in the florbetapir, florbetaben, and flutemetamol groups was 72.5, 70.7, and 69.3 years, respectively. Results from this systematic review and meta-analysis cannot, therefore, be easily extrapolated for use of amyloid imaging in early-onset AD in whom symptoms often present atypically including with aphasia, apraxia, agnosia, and visual disturbance, rather than typical amnesic syndromes. Predominant neocortical pathology, sparing the hippocampi, may manifest with a different pattern of biomarkers to disease in older age. The diagnostic utility of amyloid imaging in early-onset disease, therefore, requires separate investigation. Other areas requiring further investigation are the effectiveness, including cost-effectiveness, of amyloid imaging as compared to other currently available diagnostic tools (including CSF biomarkers, ¹⁸F-fluorodeoxyglucose positron emission tomography, and single photon emission computed tomography imaging), which are currently lacking.

5. Conclusion

This systematic review and meta-analysis has demonstrated favorable sensitivity and specificity of amyloid imaging with novel fluorine tracers in diagnosis of AD, supporting their use as an adjunct in clinical practice. It has, however, also highlighted a number of areas of uncertainty suggesting the need for further well-powered

longitudinal studies including correctly phenotyped patients, correlating with structural imaging and CSF biomarkers, neuropsychology assessment, *APOE* ϵ 4 status, and ultimately, histopathological disease confirmation, before they can be recommended for routine and widespread use.

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Supplementary data

Supplementary data related to this article can be found online at <http://dx.doi.org/10.1016/j.dadm.2014.11.004>.

RESEARCH IN CONTEXT

1. Systematic review: We searched the Medical Literature Analysis and Retrieval System Online (MEDLINE) and the Excerpta Medica Database (EMBASE) for human studies published from January 1980 to March 2014, inclusive of all languages. Search terms were “dementia”; “amyloid” or “positron emission tomography”; “florbetapir” or “florbetaben” or “flutemetamol”; “sensitivity” and “specificity” or “diagnosis.” Articles fulfilling study inclusion criteria were systematically evaluated using the STARD checklist.
2. Interpretation: To our knowledge, this is the first systematic review and meta-analysis investigating the diagnostic utility of ^{18}F -labeled tracers in Alzheimer's disease (AD); our study demonstrated favorable sensitivity and specificity, supporting their use in clinical practice.
3. Future directions: Our study has highlighted areas of uncertainty suggesting the need for well-powered prospective studies with postmortem histopathology as a diagnostic gold standard. Further investigation is required to evaluate uncertainties including, whether *APOE* ϵ 4 status influences imaging results and if ^{18}F imaging can successfully discriminate between different dementias.

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